

07/28/00
Jc715 U.S. PTO

UTILITY PATENT APPLICATION
UNDER 37 CFR 1.53(b)

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington D.C. 20231

Case Docket No. 112910.3302

Sir:

Transmitted herewith for filing is the patent application of:

INVENTOR: John J. MURPHY and Kay Jorgenson D'ORLANDO
FOR: METHODS AND COMPOSITIONS FOR ALLEVIATING STUTTERING

Jc542 U.S. PTO
09/628803
07/28/00

Enclosed are:

- ☒ 31 pages of specification, claims, abstract
- ☒ Copy of Declaration & Power of Attorney from priority application
- ☒ Priority Claimed from US Application No. 09/362,691 filed July 29, 1999, which has been converted to a Provisional application under the provisions of 37 C.F.R. § (c)(2).
- ☐ Certified copy of _____
- ☐ _____ sheets of formal drawing
- ☒ An assignment of the invention to Interneuron Pharmaceuticals, Inc. and the assignment recordation fee
- ☒ Return Receipt Postcard
- ☐ Information Disclosure Statement, Form PTO-1449
- ☐ Copies of IDS Citations
- ☒ Preliminary Amendment
- ☒ Copy of Small Entity Declaration from priority application

The filing fee has been calculated as shown below:

| (1) FOR | (2) NO. FILED | (3) NO. EXTRA | (4) RATE | (5) AMOUNT |
|--|------------------|------------------|--------------|---------------------|
| TOTAL CLAIMS | 33 | -20 | 13 | x \$9.00 = \$117.00 |
| INDEPENDENT CLAIMS | 4 | -3 | 1 | x \$39.00 = \$39.00 |
| MULTIPLE DEPENDENT CLAIM(S) (If applicable) | | | + \$130.00 = | 00.00 |
| | | | BASIC FEE | \$ 345.00 |
| Total of above calculations = | | | | \$501.00 |

09628803-072800

Docket No.: 112910.3302

[X] Assignment & Recording Fee \$40.00

TOTAL FEE \$541.00

[X] Please charge my Deposit Account No. 50-0436 in the amount of \$541.00. A duplicate copy of this sheet is enclosed.

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[X] Any additional filing fees required under 37 CFR 1.16.


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[X] Any patent application processing fees under 37 CFR 1.17.

[X] Any filing fees under 37 CFR 1.16 for presentation of extra claims.

Respectfully submitted,

PEPPER, HAMILTON LLP


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July 28, 2000
DC: #156624 v1 (3C%_01!.WPD)

Applicant or Patentee: John J. Murphy and Kay Jorgenson D'OrlandoAttorney's Docket No.: 112910-3300

Serial or Patent No.: _____

Filed or Issued: _____

For: METHODS AND COMPOSITIONS FOR ALLEVIATING STUTTERING

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.9(d) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

- ☐ the owner of the small business concern identified below;
☒ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF ORGANIZATION: Interneuron Pharmaceuticals, Inc.ADDRESS OF ORGANIZATION: 99 Hayden Avenue, Suite 200, Lexington, MA 02421

I hereby declare that the above identified small business concern qualified as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled by inventor(s) described in

- ☒ the specification filed herewith.
☐ application Serial No. _____
☐ patent no. _____, issued _____

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e). *NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention availing to their status as small entities. (37 CFR 1.27)

NAME _____
 ADDRESS _____
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

NAME _____
 ADDRESS _____
☐ INDIVIDUAL ☐ SMALL BUSINESS CONCERN ☐ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Glenn L. CooperTITLE IN ORGANIZATION: Chief Executive OfficerADDRESS OF PERSON SIGNING: 99 Hayden Avenue, Suite 200, Lexington, MA 02421SIGNATURE: Glenn L. CooperDATE: 7/29/99

DC: #111749 v1 (2/99011.WPD)

Docket No.: 112910.3302

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

MURPHY et al.

Serial No.

Group Art Unit:

Filed:

Examiner:

For: METHODS AND COMPOSITIONS FOR ALLEVIATING STUTTERING

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Preliminary to examination of the above-referenced application, please amend the application as follows:

IN THE SPECIFICATION:

Please amend the specification as follows:

Page 2, after the title, please insert

--Related Applications

This application claims priority from U.S. Application No. 09/362,691, filed July 29, 1999, which has been converted to a Provisional Application under the provisions of 37 C.F.R. § (c)(2), incorporated herein by reference.--

AUTHORIZATION

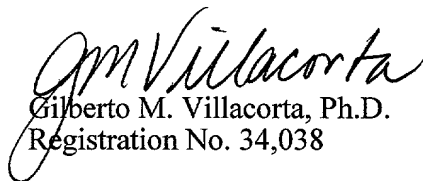
The Commissioner is hereby authorized to charge any additional fees which may be required for this Amendment, or credit any overpayment to deposit account no. 50-0436.

Docket No.: 112910.3302

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to deposit account no. 50-0436.

Respectfully Submitted,

PEPPER HAMILTON LLP


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DC: #156625 v1 (3C%P011.WPD)

An Application for a U.S. Patent

**Title: METHODS AND COMPOSITIONS FOR
ALLEVIATING STUTTERING**

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METHODS AND COMPOSITIONS FOR ALLEVIATING STUTTERING

1. Field of the Invention

5 The present invention relates generally to methods for treating stuttering. The invention also relates to pharmaceutical compositions for treating stuttering, comprising gamma-aminobutyric acid modulators and pharmaceutically acceptable salts thereof, including the cyclopyrrolones, notably pagoclone [(+)-2-(7-chloro-1,8-naphthyridine-2-yl)-3-(5-methyl-2-oxo-hexyl)-1-isoindolinone], alone or in combination with one or more
10 pharmaceutically active agents, and a pharmaceutically acceptable carrier.

2. Background of the Invention

2.1. *Developmental and Neurogenic Stuttering.*

15 Stuttering is a poorly understood condition marked by frequent repetitions or prolongations of sounds, and an impaired fluency of speech. Accessory features of stuttering, possibly resulting from the attempts of the stutterer to control the stuttering, include blocks in the flow of speech sounds, swallowing, grimacing, tremors of the jaw and tongue, coughing, rapid eye blinking, and jerking movements of the arm or upper trunk. (Brady, J. *Am J Psychiatry*, **1991**, 148, 1309). One form, developmental
20 stuttering, often appears in early human childhood or adolescence, and affects predominantly males. An estimated three million Americans are affected and the condition is not dependent on language type or cultural background. A less frequent type is neurogenic stuttering, often a result of head trauma or stroke. Subtle differences between neurogenic and developmental dysfluency may be observed, for example in the
25 repetitive reading test, where sufferers of developmental stuttering often improve by the tenth reading of a passage, but sufferers of neurogenic stuttering do not. A third type is drug-induced stuttering, an increasingly frequent problem.

In the past, stutterers have been treated by a wide variety of methods devised by some of the best minds of the time. Both Hippocrates and Hieronymus Mercurialis

recommended oral or head surgeries or mutilations. In this century, psychiatric treatments have been tried ranging from operant reinforcement to psychotherapy for presumed unconscious conflicts. However, those who stutter are remarkably well-adjusted, and are similar to those who do not stutter in personality traits. Current
5 methods include speech training and pharmaceutical intervention. The improvement for patients, unfortunately, has been limited.

The spectrum of experimental pharmaceutical interventions has been broad. At times, carbon dioxide inhalation, stimulants (notably methamphetamine), sedatives (in particular, phenobarbital combined with belladonna and ergotamine), an early
10 antihistamine (hydroxyzine), bromides, thiamine supplements, an antihypertensive (reserpine), the tranquilizer meprobamate, anxiolytics (in particular, benzodiazepines), neuroleptics (including thioridazine, chlorpromazine and trifluoperazine), verapamil, beta-adrenergic blockers (including propranolol, betaxolol, and oxprenolol), an anticonvulsant (carbamazepine), and cholinergic agents (neostigmine and bethanecol)
15 have been tried for stuttering, but all with unsustainable success. Haloperidol has been particularly well studied as an agent for the attenuation of stuttering.

Notably Wells, P. G. et al. *Br J Psychiatry* **1971**, *119*, 603, reported a placebo-controlled, double-blind study. Wells et al., randomized patients into treatment groups, included objective measures of speech, and found a significant improvement over an
20 eight-week course. Objective criteria in such studies include the length of time to read a standard passage, the number of syllabic repetitions in the process of conveying specific information, the time to explain a solution to a puzzle, and the like. Subsequent studies support a significant improvement in the accessory symptoms of stuttering, including rapid blinking and jerking movements of the upper body, but patient compliance is low
25 because of side-effects including dizziness and dysphoric “medicine-head” symptoms. More significant and disturbing are the long-term detrimental effects haloperidol and other neuroleptics have on voluntary muscle function, known as tardive dyskinesia.

2.2 The GABA_A Neuronal Pathway.

One of the main neurotransmitters involved in inhibitory neuronal pathways is
30 gamma-aminobutyric acid or GABA. GABA appears to function mainly at two types of

receptors, termed GABA_A and GABA_B receptors, that have different structures. The GABA_A receptor is a GABA-gated chloride ion channel and the GABA_B receptor is a G-protein coupled regulator of potassium conductance. GABA receptors can be modulated by several classes of pharmacologic agents, notably the benzodiazepines, the barbiturates, convulsants, and neurosteroids of the class epiallopregnanolone or epalons. These classes of agents appear to act at different, discrete sites on the GABA_A receptor. Thus, the diversity of effects expressed by these agents ranges from the tranquilizing effects of benzodiazepines, and the sedative effects of barbiturates to the convulsant effects of *t*-butyl-bicyclophosphorothionate (TBPS), which may act on GABA_A receptors associated with clathrin-coated vesicles. The cyclopyrrolones have demonstrated high affinity for the benzodiazepine binding site on the GABA_A receptor. Some cyclopyrrolones, e.g., pagoclone, have a pharmacological profile consistent with that of a partial agonist at this site. Partial agonists can be efficacious in producing some effects, e.g., anxiolysis, in common with full agonists, but may be less effective in producing others, e.g., sedation. Antagonists, or “blockers,” on the other hand, counteract the action of endogenous GABA and exogenous agonists. Inverse agonists decrease the inherent or constitutive stimulation by a receptor in the absence of an agonist. Modulator is a term that includes agonist, partial agonist, inverse agonist, antagonist, neurotransmitter, reuptake inhibitor, and degradation inhibitor. Antagonists are often relatively specific to a particular class of agonists. For example, flumazenil, a benzodiazepine antagonist, blocks the function of benzodiazepines including flunitrazepam, diazepam, pinazepam, prazepam, halazepam, camazepam, and flurazepam.

GABA_A receptor modulators, especially agonists and partial agonists, are also known to act as antipobics, myorelaxants, anti-epileptics, and by other means. GABA_A receptor modulators act as myorelaxants by decreasing muscle stiffness, decreasing tonus, and reducing voluntary muscle contraction in spasticity. Also some GABA_A modulators have hypnotic, sleep-inducing, amnestic, sedative, and/or anti-convulsant effects. Antagonists of GABA_A receptor function tend to block these effects and may even be anxiogenic or proconvulsant in some individuals.

Many of the GABA_A agonists, in particular the benzodiazepines and the

cyclopyrrolones, act to reduce anxiety and induce a sense of calm. In consequence, these agents are termed anxiolytics. It has long been thought that anxiety is a component of stuttering, although the cellular bases for anxiety and stuttering are not at all clear. In contrast, however, the results of placebo-controlled studies of benzodiazepines on
5 stuttering have been inconsistent and disappointing (Brady, *supra*).

2.3 *Drug-induced Stuttering.*

A different approach, that of evaluating drug-induced stuttering, has led to some useful observations, but no cure. Part of the confusion is that many drugs induce stuttering. Several workers have reported that phenothiazines induce stuttering, whether
10 administered alone or with other agents. This drug-induced stuttering was accompanied by akathisia, or a “can’t sit still” syndrome. Rentschler, G. J. et al., *J Fluency Disord* **1984**, 9, 265 and Elliot, R.I. et al., *J Clin Psychopharmacol* **1985**, 5, 159, report stuttering in response to benzodiazepines. Alprazolam, a potent anxiolytic, can induce stuttering (Elliot, *supra*).

15 Most of the other cases of drug-induced stuttering are related to inhibition of serotonin uptake, usually with the drugs sertraline or fluoxetine (Brady, J.P. *J Clin Psychopharmacol* **1988**, 18, 50), which are also considered to be anxiolytics. The induced stuttering was frequently accompanied by akathisia in these cases as well.

Thus, the state of the art underscores the prevailing and unfilled need for an
20 effective pharmacologic treatment of stuttering. Indeed, the long-standing effort to cure or relieve stuttering has engaged many clinicians over decades, centuries, and even millennia. At least two conclusions may be reached from the wide range of pharmacologic treatments attempted for stuttering. The first is that no clear understanding of the underlying basis for stuttering exists. The study of stuttering is
25 particularly intractable because there exist no animal models and the evaluation of improvement in stuttering is fraught with subjective criteria. The second is that no known agent, or combination of agents, is effective in treating this widespread difficulty.

3. Summary of the Invention

In a general aspect, the present invention relates to a method for alleviating stuttering, which comprises administering a preparation including an effective amount of one or more GABA receptor modulators.

5 It is an object of the invention to provide a method for alleviating stuttering, which comprises administering a therapeutically effective dose of a preparation selected from the class of benzodiazepines. Use of active metabolites, active enantiomers, active racemic mixtures, or pharmaceutically acceptable salts of benzodiazepines, as an anti-stuttering medication is contemplated.

10 It is another object of the invention to provide a method for alleviating stuttering, which comprises administering a therapeutically effective dose of a preparation selected from the class of cyclopyrrolones. The class of cyclopyrrolones includes, but is in no way limited to, pagoclone, suriclone (4-methyl-1-piperazinecarboxylic acid 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester),
15 zopiclone (4-methyl-1-piperazinecarboxylic acid 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo-[3.4]pyrazin-5-yl ester), and the compound of US Patent No. 5,676,831. Use of active metabolites, active enantiomers, active racemic mixtures, or pharmaceutically acceptable salts of cyclopyrrolones, as an anti-stuttering medication is contemplated.

20 In a yet further object of the invention, pagoclone, its active metabolite, its active enantiomer, an active racemic mixture comprising pagoclone, or pharmaceutically acceptable salts thereof, are contemplated as an anti-stuttering medication.

The present invention is useful for treating, alleviating or preventing stuttering. In an embodiment of the invention, the stuttering can be characterized as being
25 developmental, neurogenic or drug-induced stuttering. Likewise, stuttering is understood to include common stuttering, motor tic, clonic stuttering, dysfluency, speech blockage, impaired phonation, dysarthria, Tourette's syndrome, developmental stuttering, neurogenic stuttering, drug-induced stuttering, logospasm, and the like. There can be different organic, genetic, or developmental origins of the stuttering.

In addition, the present invention also contemplates a pharmaceutical composition suitable for alleviating stuttering in a person afflicted with stuttering which comprises (i) at least one GABA_A receptor modulator, active enantiomer, active metabolite, or pharmaceutically acceptable salt thereof; (ii) at least a second pharmaceutically active agent; and (iii) a pharmaceutically acceptable carrier.

In a more particular aspect, the invention relates to a pharmaceutical composition comprising a GABA_A modulator, including but not limited to pagoclone; suriclone (4-methyl-1-piperazinecarboxylic acid 6-(7-chloro-1,8-naphthyridin-2-yl)-2,3,6,7-tetrahydro-7-oxo-5H-1,4-dithiino[2,3-c]pyrrol-5-yl ester); zopiclone (4-methyl-1-piperazinecarboxylic acid 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo-[3.4]pyrazin-5-yl ester); 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, their active enantiomers, their metabolites, or pharmaceutically acceptable salts thereof, alone or in combination with an agent selected from the group consisting of: analgesics, abortifacients, ACE inhibitors, alpha-adrenergic agonists, alpha-adrenergic antagonists, beta-adrenergic agonists, beta-adrenergic antagonists, adrenocortical steroids, adrenocortical suppressants, adrenocorticotrophic hormone, alcohol deterrents, aldose reductase inhibitors, aldosterone antagonists, 5'-alpha reductase inhibitors, analgesics, androgens, anesthetics, antacids, anthelmintics, antiallergics, antialopecia agents, antiamebics, antiandrogens, antianginals, antiarrhythmics, antiatherosclerotics, antiarthritics, antiasthmatics, antibiotics, anticholelithogenics, anticholesterimics, anticholinergics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antidiarrheals, antidiuretics, antidyskinetics, antieczemicals, antiemetics, antiepileptics, antiestrogens, antifibrotics, antiflatulents, antifungals, antiglaucoma agents, antihistaminics, antihypertensives, antihypotensives, anti-inflammatories, antimalarials, antimanics, antimigraines, antineoplastics, antiosteoporotics, antiprotozoals, antipruritics, antipsychotics, antivirals, other anxiolytics, bronchodilators, vasodilators, contraceptives, decongestants, diuretics, antimigraines, immunosuppressants, inotropic agents, laxatives, muscle relaxants, supplements, prophylactics of urinary tract infections, and vitamins.

A further object of the invention relates to administration of independent

pharmaceutical preparations to the same patient at the same time or different times, preferably at about the same time, and by the same or different modes of administration, where one pharmaceutical preparation comprises a GABA_A receptor modulator and the second pharmaceutical preparation comprises a different agent.

5

4. Detailed Description of the Invention

The present invention contemplates a method of alleviating stuttering in a person, comprising administering an effective stuttering alleviating amount of at least one GABA receptor modulator, an enantiomer of the modulator, an active metabolite of the
10 modulator, or a pharmaceutically acceptable salt of the modulator. One embodiment is a GABA receptor modulator effective at the receptor subtype A.

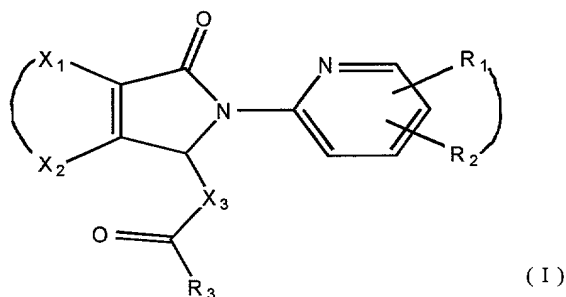
A method of the present invention includes the treatment of the developmental stuttering and dysfluency that manifests itself, commonly, in adolescence or childhood. Another method of the present invention includes the treatment of stuttering and
15 dysfluency that can occur after trauma to head and body tissues, e.g., those resulting from surgery, injuries, etc. Hence, the pharmaceutical treatment according to the present invention can be administered prior to or after surgery. The present invention contemplates the treatment of drug-induced stuttering as yet another embodiment.

Any mode of administration may be used. It is preferred, however, that the mode
20 of administration is selected from parenteral, oral, vaginal, rectal, nasal, buccal, intravenous, intramuscular, subcutaneous, intrathecal, epidural, intracerebroventricular, transdermal, or combinations thereof. The GABA_A receptor modulator, enantiomer of the modulator, active metabolite of the modulator, or pharmaceutically acceptable salt of the modulator, can act in the central nervous system, including spinal cord, or in the
25 peripheral nervous system, the neuro-muscular system or elsewhere. These agents can have transient action, sustained action or persistent action.

The means of administration will be evident to one skilled in the art, who will know, for example, that some agents must be brain permeant, either in and of themselves, or facilitated by a suitable device or carrier, whereas others should not cross the blood
30 brain barrier.

A wide variety of agents active at GABA_A receptors are suitable for use in the present invention, including cyclopyrrolones, benzodiazepines, general anesthetics, barbiturates, and, neurosteroids, alone or in combination. Suitable components are: allopregnanolone, alphaxalone, alprozolan, amobarbital, aprobarbital, avermectin B, ±
5 baclofen, bicuculline, butabarbital, butalbital, camazepam, cloflubicyne, chlordiazepoxide, clorazepam, chlorazepate, diazepam, diazepam binding inhibitory protein, diazepam binding inhibitory protein fragment, dihydroepiandrosterone, epiallopregnanolone, estazolam, etbicuphat, etbicythionat, etomidate, flucybene, flunitrazepam, flurazepam, halazepam, D-β-hydrastine, isobicyphat, lorazepam,
10 mebicuphat, mephobarbital, methohexital, midazolam, oxazepam, pagoclone, pentobarbitone, pentobarbital, phenobarbital, picrotoxinin, picrotin, pinazepam, prazepam, pregnanolone, pregnenolone, progesterone, propofol, propylbicyphat, quazepam, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, also known as RP59037; 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-
15 acetamidobutyrate also known as RP60503, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone also known as RPR101769, secobarbital, suriclone, tenazepam, tetrahydrodeoxycorticosterone, tetramethylene sulfotetramide, thiopental, triazolam, zopiclone, and pharmaceutically acceptable salts thereof. Active enantiomers, active metabolites and active racemates of these agents, if they exist, are
20 equally suitable.

The present invention provides a new method of treatment of stuttering using pharmaceutical compounds that preferentially modulate GABA_A receptors. In particular, the useful compounds of the invention are cyclopyrrolones according to Formula I, metabolites thereof, enantiomers thereof, racemates thereof, and salts including acid
25 addition salts thereof, alone or in conjunction with one or more other therapeutic agents:



wherein:

(a) R_1 and R_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen; alkyl having 1 to 8 carbon atoms; alkyl having 1 to 8 carbon atoms, and having at least one of nitrogen, oxygen, sulfur, or phosphorus; aryl having 1 to 8 carbon atoms; and aryl having 1 to 8 carbon atoms and having at least one nitrogen, oxygen, sulfur, or phosphorus;

(b) R_3 is selected from the group of substituents consisting of: alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the proviso that each of the foregoing R_3 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms, aryl, alkaryl, piperazinyl, and methyl-piperazinyl;

(c) X_1 and X_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl

having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing X₁ and X₂ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms; and

(d) X₃ is selected from the group consisting of: a methylene; —C(HR₄)— where R₄ is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R₄ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; amino; —N(R₅)— where R₅ is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R₅ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; sulfur; phosphorus; and oxygen group; pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

The R₁ and R₂ substituents can be on positions 3, 4, 5, or 6 of the ring.

The invention includes compounds having the structural formula I and the acid addition salts thereof. For medical use, the pharmaceutically acceptable acid addition

salts are preferred. The pharmaceutically acceptable acid addition salts are those salts in which the anion does not contribute significantly to the toxicity or pharmacological activity of the salt, and as such, they are the pharmacological equivalents of the bases having the foregoing structural formulas. In some instances, the salts have physical properties which make them more desirable for pharmaceutical formulation purposes such as solubility, lack of hygroscopicity, compressibility with respect to tablet formation and compatibility with other ingredients with which the substances may be used for pharmaceutical purposes. Acid addition salts which do not meet the foregoing criteria for pharmaceutical acceptability, for instance as to toxicity, are sometimes useful as intermediates for isolation and purification of the present substances or for other chemical synthetic purposes such as separation of optical isomers. Such salts are also part of the invention.

The acid addition salts are made by reaction of a base of the structural formula I with the acid, preferably by contact in solution. They also are made by metathesis or treatment with an anion exchange resin whereby the anion of one salt of the substance is replaced by another anion under conditions which allows for separation of the undesired species such as by precipitation from solution or extraction into a solvent or elution from or retention on an anion exchange resin. Pharmaceutically acceptable acids for the purposes of salt formation include hydrochloric, hydrobromic, hydroiodic, citric, acetic, benzoic, phosphoric, nitric, mucic, isethionic, methanesulfonic, p-toluenesulfonic, glucosaccharic, palmitic, heptanoic, oxalic, cyclamic, succinic, malic, fumaric, mandelic, malonic, and others.

The compounds of the present invention shown by the structural formula I contain an asymmetric carbon atom in the cyclopyrrolone ring and occur as optically active isomers as well as racemic mixtures thereof. The present invention is intended to include each of the optically pure, optically active and racemic forms. Some of the substances of the present invention contain an asymmetric carbon atom in the X₁, X₂, R₁, R₂, or R₃ substituents in formula I, and diastereoisomeric pairs of racemates exist. These forms are also contemplated and included in the methods of the present invention.

Resolution of racemic mixtures to provide the optically active isomers of the foregoing compounds is carried out, for example, by forming a salt with an optically active acid many of which are known to those skilled in the art such as optically active tartaric, mandelic, cholic, O,O-di-p-toluoyl tartaric, and O,O-dibenzoyl tartaric acids, or other acids conventionally employed for this purpose. Separation of optical isomers can be accomplished as disclosed in United States Patent 4,960,779 which is incorporated herein by reference.

For the preparation of pharmaceutical compositions containing the compounds of Formula I in the form of dosage units for oral administration, the compound is mixed with a solid, pulverulent carrier such as lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives, or gelatin, as well as with glidants such as magnesium stearate, calcium stearate, polyethylene glycol waxes or the like and pressed into tablets. The tablets are used uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. When coated tablets are desired, the above prepared core is coated with a concentrated solution of sugar, which solution may contain e.g., gum arabic, gelatin, talc, titanium dioxide or the like. Furthermore, the tablets are coated with a lacquer dissolved in an easily volatile organic solvent or mixture of solvents and if desired, dye is added to this coating.

In the preparation of soft gelatin capsules consisting of gelatin and e.g., glycerine and the like, the active ingredient is mixed with a vegetable oil and encapsulated in conventional manner. Hard gelatin capsules may contain granules of the active ingredient in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, starch (such as e.g. potato starch, corn starch, or amylopectin), cellulose derivatives or gelatin.

Dose units for rectal administration may be prepared in the form of suppositories containing the compound in a mixture with a neutral fat base, or in the form of a gelatin-rectal capsule with a mixture of vegetable oil or paraffin oil.

Liquid preparations suitable for oral administration are suspensions, syrups and elixirs containing from about 0.2% by weight to about 20% by weight of the active ingredient.

5 A suitable injectible composition is comprised of an aqueous solution of a water soluble pharmaceutically acceptable acid addition salt adjusted to physiologically acceptable pH.

The present invention relates to a pharmaceutical composition for alleviating stuttering, which comprises: (a) an effective amount of a first active ingredient, which comprises at least one GABA_A receptor modulator, including, but not limited to the
10 cyclopyrrolone class of agents, enantiomers, metabolites, and pharmaceutically acceptable salts thereof; optionally, (b) an effective amount of a second active agent; and optionally (c) a pharmaceutically acceptable carrier.

The terms "effective amount," "therapeutically effective amount," or "pharmaceutically effective amount" of a compound in unit dosage form of the
15 composition depends upon a number of factors. Included among these factors is the quantity of the other ingredients when used. An effective amount of the active ingredient ranges from about 1% to about 100% by weight based on the total weight of the composition but, in any event, is sufficient to observe the anticipated benefit.

By "pharmaceutically acceptable carrier" is meant solid or liquid filler, diluent, or
20 encapsulating substance, which may be safely used in systemic or topical administration. Depending on the particular route of administration, a variety of pharmaceutically acceptable carriers well known in the art may be used, including solid or liquid fillers, diluents, hydrotropies, surface active agents, and encapsulating substances. The amount of a carrier employed in conjunction with the GABA_A receptor modulator is sufficient to
25 provide practical quantity of material per unit dose of GABA_A receptor modulator. Pharmaceutically acceptable carriers for systemic administration, which may be incorporated in the composition of the invention, include sugar, starches, cellulose, vegetable oils, mineral oils, buffers, polyols, alginic acid and the like. Specific pharmaceutically acceptable carriers are described in U.S. Pat. No. 4,401,663; European
30 Patent Application No. 089710; and European Patent Application No. 0068592, which

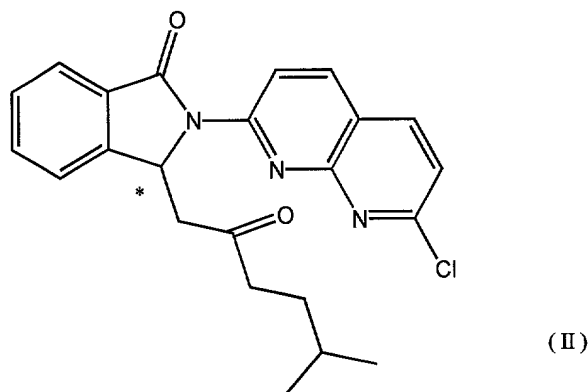
are incorporated herein by reference.

Carriers for parenteral administration may include propylene glycol, pyrrolidone, ethyl oleate, aqueous ethanol and combinations thereof.

Still other representative carriers include acacia, agar, alginates,

- 5 hydroxyalkylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, carrageenan, powdered cellulose, guar gum, cholesterol, gelatin, gum agar, gum arabic, gum karaya, gum ghatti, locust bean gum, octoxynol-9, oleyl alcohol, pectin, poly(acrylic acid) and its homologs, polyethylene glycol, polyvinyl alcohol, polyacrylamide, sodium lauryl sulfate, poly(ethylene oxide),
10 polyvinylpyrrolidone, glycol monostearate, propylene glycol monostearate, xanthan gum, tragacanth, sorbitan esters, stearyl alcohol, starch and its modifications. Suitable ranges vary from about 1% to about 50% by weight of the total composition.

- Preferred GABA_A receptor modulators are cyclopyrrolones, including, but not limited to, pagoclone; zopiclone; suriclone; 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-
15 4- acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, active metabolites thereof, enantiomers thereof, and pharmaceutically acceptable salts thereof. The most preferred GABA_A receptor modulator is pagoclone, as shown by formula II, where the asterisk indicates the chiral
20 atom, and pharmaceutically acceptable salts thereof.



GABA_A modulators suitable for use in the present invention can exist as salts. In

particular, the compounds of the invention can form acid addition salts of pharmaceutically acceptable inorganic or organic acids. Examples of suitable inorganic acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, phosphoric, or nitric acid. Examples of suitable organic acids include, but are not limited to, aliphatic or aromatic carboxylic or sulfonic acids, for example, acetic, propionic, succinic, glycolic, lactic, fumaric, tartaric, tannic, gluconic, citric, ascorbic, maleic, pyruvic, palmoic, oxalic, dioxalic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluenesulfonic, or naphthalenesulfonic acid. Preferred salts include the hydrochloride, oxalate, fumarate, citrate, tannate, or dioxalate salts.

The GABA_A receptor modulators and salts thereof are discussed in detail in Remington's Pharmaceutical Sciences (in Gennaro, A. et al., Ed., Mack Pub. Co., Easton, Pa 18th ed. 1990, 1057-1071), the relevant portions of which are incorporated herein by reference.

The pharmaceutical composition of the present invention can have a wide range of GABA_A receptor modulator dosage where a total dosage of about 0.01 to about 1000 mg is administered daily. More preferably, this dosage is about 0.1 mg to about 10 mg. The frequency of doses can vary from about one per day to about two per hour. The dosage can also be adjusted for body weight, from about 0.001 mg/ kg body weight/ day to about 1.0 mg/ kg body weight/ day.

The administration of the GABA_A receptor modulator can be by intravenous, intramuscular, subcutaneous, intrathecal, epidural, or intracerebroventricular injection, or parenterally, orally, vaginally, rectally, nasally, buccally, transdermally, and combinations thereof.

The administration of the stuttering alleviating or ameliorating substance to the patient can be conducted in conjunction with treatment for other ailments with the second active agent, or other agents. Effective dosage levels can vary widely; actual amounts will depend on the agents used and the state and diagnosis of the patient being treated. As those skilled in the art would recognize, many factors that modify the action of the stuttering alleviating composition and second active agents herein will be taken into account by the treating physician including, but not limited to, such factors as age, body

weight, sex, diet and condition of the patient, time of administration, rate and route of administration, psychiatric condition, other diseases, and so forth. Titration of dosage for individual patients, up to the maximal dose permits attainment of functionally effective doses. Optimal dosages for a given set of conditions can be ascertained by those skilled
5 in the art using conventional dosage determination tests in view of experimental data provided herein.

The stuttering alleviating substance of the instant invention will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and acceptable practice. The stuttering alleviating substance can be formulated as
10 a liquid, powder, aerosol, elixir, injectable solution, etc. Formulations for oral use can be provided as hard gelatin capsules wherein the stuttering alleviating substance is mixed with an inert solid diluent such as calcium carbonate, phosphate, or kaolin or, preferably, as soft gelatin capsules wherein the stuttering alleviating substance is mixed with an oleaginous medium, e.g., liquid paraffin or soybean oil.

Aqueous suspensions can contain the stuttering alleviating substance in an admixture with pharmaceutically acceptable excipients such as: suspending agents, like
15 carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin; or condensation products of an
20 alkaline oxide with fatty acids, e.g., polyoxyethylene stearate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol, e.g., polyoxyethylene sorbitol monooleate; or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monooleate. Such aqueous suspensions can also contain one or more
25 preservatives, e.g., ethyl or *n*-propyl-*p*-hydroxybenzoate; or one or more coloring agents, flavoring agents and sweetening agents such as saccharose, saccharin or sodium or calcium cyclamate.

In the preparation of aqueous suspensions, water is added to dispersible powders and granules to provide the stuttering alleviating substance in an admixture with
30 dispersing or wetting agent, suspending agent and one or more preservatives. Suitable

dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients include sweetening, flavoring and coloring agents. Syrups and elixirs can be formulated with sweetening agents such as glycerol, sorbitol or sucrose. Such formulations can contain demulcent, preservative, flavoring and coloring agents.

The stuttering alleviating agent can be administered in a sustained release formulation. Methods for sustained release dosage forms are advantageously provided in U.S. Pat. Nos. 4,788,055; 4,816,264; 4,828,836; 4,834,965; 4,834,985; 4,996,047; 5,071,646; and 5,133,974, which are incorporated herein by reference.

The compositions of the invention have pharmacological advantages that render them useful for alleviating stuttering. In this application, at least one GABA receptor modulator and one or more second active agent may be administered according to any convenient or effective method for introducing foreign substances into the blood stream of mammals, such as by oral, rectal, nasal, buccal, vaginal or parenteral routes. The effective dose levels may be administered on a regimen of about 1 to about 6 times a day. The pharmaceutical formulation of the invention can be in dosage forms such as pills, capsules, powders or granules for oral administration. The compounds can be conveniently administered in unit dosage form and can be prepared by any of the methods well known in the pharmaceutical art, for example as described in Remington's Pharmaceutical Sciences, *supra*, 1451-1459, 1504-1512, 1519-1570, and 1615-1693, which are incorporated herein by reference.

The compounds of the invention can be formulated into pharmaceutical compositions of an admixture with pharmaceutically acceptable carriers. As discussed above, the compositions may be prepared for use by or in parenteral, that is, subcutaneous, intramuscular, or intravenous, administration, particularly in the form of liquid suspensions. Also, the composition can be prepared for oral administration, particularly in the form of tablets or capsules, or intranasally, particularly in the form of powders, nasal drops or aerosols. The composition can also be prepared for use in vaginal or rectal administration. Formulations for parenteral administration may contain as common excipients, sterile water, or saline, polyalkylene glycols such as polyethylene

glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Formulations for vaginal or rectal administration, e.g., suppositories may contain as excipients, for example, polyalkylene glycols such as polyethylene glycol, petroleum jelly, cocoa butter and the like. Formulations for inhalation administration may be solid and contain
5 excipients, for example, lactose, or may be aqueous or oily solutions for administration in the form of nasal drops. For buccal administration, typical excipients include sugars, calcium stearate, magnesium stearate, pregelatinated starch and the like.

For oral administration, a pharmaceutically acceptable composition can be formed by incorporation of any of the normally employed excipients, oral dose extenders or
10 carriers such as for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate and the like. Such compositions can take the form of solution, suspension, tablets, pills, capsules, powders, sustained release formulations and the like.

To produce tablets or dragée cores, the active substances are combined with, e.g.,
15 solid pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch, amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatin, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycol of suitable molecular weight to form tablets or dragée cores. The latter are coated, e.g., with concentrated sugar solutions
20 which can also contain, e.g., gum arabic, talcum, titanium dioxide, or with lacquer dissolved in a mixture of solvents. Other suitable oral dosage units are hard gelatin capsules as well as soft, closed capsules from a gelatin softener such as glycerol.

Examples of dosage units for rectal administration are suppositories that comprise a combination of at least one GABA_A receptor modulator, one or more second active
25 agents and a carrier suppository foundation. Also suitable are a gelatin rectal capsules, which contain a combination of at least one of the above substances with polyethylene glycol of suitable molecular weight as carrier.

Ampoules for parenteral, particularly intramuscular and also intravenous administration, preferably contain at least one GABA_A receptor modulator and one or
30 more second active agents. If necessary, suitable stabilizing agents and/or buffer

substances are added to the ampule solutions.

These compounds can be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers can be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, peanut oil, olive oil, sesame oil, vegetable oil, mineral oil, soybean oil, cottonseed oil, glycerin, saline, ethanol, and water. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation is in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation can be administered directly by mouth or filled into a soft gelatin capsule.

5. Examples

The following specific examples are provided to better assist the reader in the various aspects of practicing the present invention. As these specific examples are merely illustrative, nothing in the following descriptions should be construed as limiting the invention in any way. Such limitations are, of course, defined solely by the accompanying claims.

6.1 *Improvement of the Stuttering of a Patient Treated with Pagoclone.*

A 26-year old female patient is enrolled in a clinical trial examining the efficacy and safety of pagoclone, a drug which works at the GABA_A receptor, in the treatment of panic disorder, an anxiety disorder. She experiences a significant reduction in her fairly severe stuttering problem while she is taking the pagoclone. The double-blind placebo-controlled trial conceals the drug type until the conclusion of the trial.

During the trial the patient is taking 0.60 mg pagoclone/ day (0.20 mg t.i.d.). The patient had never before experienced this sort of an effect on her stuttering and she had taken, in the past, other anti-anxiety medications for her psychiatric condition, none of which had such an effect on her stuttering. During the trial, both she and the clinician treating her in the clinical trial notice the reduction in her stuttering, which is documented at her week 2 visit. Her stuttering returns to the pre-drug level within a day of stopping the pagoclone. She also experiences a reduction in her anxiety and improvement in her psychiatric condition. During the trial she also is taking ibuprofen and a prophylactic for urinary tract infections.

6.2 *Large-Scale Trial Treatment, With Pagoclone, Of Patients Suffering From Developmental Stuttering.*

Patients with stuttering problems are enrolled in a clinical trial examining the efficacy and safety of pagoclone in the treatment of developmental stuttering. The open-label trial is administered by physicians. During the trial one group of twenty patients is taking 0.60 mg pagoclone/ day (0.20 mg t.i.d.), another group is taking 0.20 mg pagoclone/ day, and another group is taking a placebo. The patients have never before experienced relief of stuttering by a medication. During the trial, both the patients and the clinicians treating them in the clinical trial monitor the stuttering by a battery of objective tests, and document each case.

6.3 *Large-Scale Treatment, With Selected GABA_A Modulators, Of Patients Suffering From Stuttering.*

Patients with stuttering problems are enrolled in a clinical trial examining the efficacy and safety of zopiclone, suriclone, diazepam, propofol, alphaxalone, and pentobarbital, drugs which work at the GABA_A receptor, in the treatment of developmental stuttering. The patients are randomly assigned to one of eight groups. The double-blind placebo-controlled trial conceals the drug type until the conclusion of the trial. During the trial each group of patients is taking a therapeutically effective dose of one agent or is taking the placebo. The patients have never before experienced relief of stuttering by a medication. During the trial, both the patients and the clinicians treating them in the clinical trial monitor the stuttering by objective evaluations of

dysfluency, and document each case.

6.4 *Large-Scale Trial Treatment, With Pagoclone And A Second Active Agent,
Of Patients Suffering From Stuttering.*

Patients with stuttering problems are enrolled in a clinical trial examining
5 the efficacy and safety of pagoclone and a second active agent in the treatment of
developmental stuttering. The second agents are ibuprofen, UTI Plus, propranolol,
minoxidil, estrogen, citicoline, ergotamine, and pregnanolone. Patients are randomly
assigned to one of nine groups. The double-blind placebo-controlled trial conceals the
drug type until the conclusion of the trial. During the trial all patients are taking 0.01 mg
10 pagoclone/ kg body weight/ day. Each group is provided a pharmaceutically effective
daily dose of one of the eight second active agents, and one group is provided a placebo.
The patients have never before experienced relief of stuttering from a medication.
During the trial, both the patients and the clinicians treating them in the clinical trial
monitor the stuttering by a battery of objective criteria, and document each case.

15

WHAT IS CLAIMED IS:

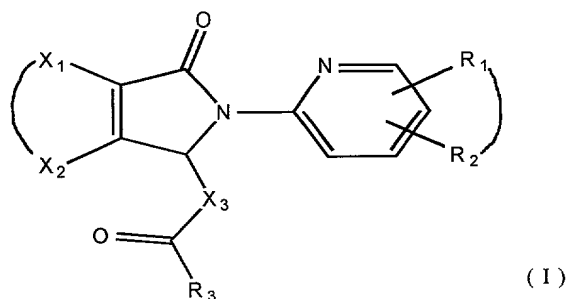
1. A method for alleviating stuttering, in a subject in need thereof,
comprising:

5 administering a therapeutically effective dose of a gamma-aminobutyric acid
receptor modulator, its pharmaceutically acceptable salts, enantiomers, or metabolites
thereof.

2. The method according to claim 1,

wherein said modulator comprises: allopregnanolone, alphaxalone, alprozolam,
10 amobarbital, aprobarbital, avermectin B, \pm baclofen, bicuculline, butabarbital, butalbital,
camazepam, cloflubicyne, chlordiazepoxide, clorazepam, chlorazepate, diazepam,
diazepam binding inhibitory protein, diazepam binding inhibitory protein fragment,
dihydroepiandrosterone, epiallopregnanolone, estazolam, etbicuphat, etbicythionat,
etomidate, flucybene, flunitrazepam, flurazepam, halazepam, D- β -hydrastine,
15 isobicyphat, lorazepam, mebicyphat, mephobarbital, methohexital, midazolam,
oxazepam, pagoclone, pentobarbitone, pentobarbital, phenobarbital, picrotoxinin,
picrotin, pinazepam, prazepam, pregnanolone, pregnenolone, progesterone, propofol,
propylbicyphat, quazepam, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-
oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-
20 acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-
oxohexyl)-1-isoindolinone, secobarbital, suriclone, tenazepam,
tetrahydrodeoxycorticosterone, tetramethylene sulfotetramide, thiopental, triazolam,
zopiclone, pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites
thereof.

3. The method according to claim 1, wherein the modulator has the formula (I):



wherein:

- (a) R_1 and R_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen; alkyl having 1 to 8 carbon atoms; alkyl having 1 to 8 carbon atoms, and having at least one of nitrogen, oxygen, sulfur, or phosphorus; aryl having 1 to 8 carbon atoms; and aryl having 1 to 8 carbon atoms and having at least one nitrogen, oxygen, sulfur, or phosphorus;
- (b) R_3 is selected from the group of substituents consisting of: alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the proviso that each of the foregoing R_3 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms, aryl, alkaryl, piperazinyl, and methyl-piperazinyl;
- (c) X_1 and X_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl

having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing X₁ and X₂ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms; and

(d) X₃ is selected from the group consisting of: a methylene; —C(HR₄)— where R₄ is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R₄ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; amino; —N(R₅)— where R₅ is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R₅ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; sulfur; phosphorus; and oxygen group; pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

4. The method according to claim 3, wherein R₁ and R₂ are covalently bonded to form a polycyclic structure.

5. The method according to claim 3, wherein the cycloalkyl of R₃, R₄, R₅, X₁,

and X₂ are the same or different, and each have up to 3 alkyl substituents.

6. The method according to claim 3, wherein the cycloalkenyl of R₃, R₄, R₅, X₁, and X₂ are the same or different, and each have up to 3 alkyl substituents.

7. The method according to claim 3, wherein the cycloalkylalkyl of R₃, R₄, R₅, X₁, and X₂ are the same or different and each have up to 3 alkyl substituents.

8. The method according to claim 3, wherein the cycloalkenylalkyl of R₃, R₄, R₅, X₁, and X₂ are the same or different and each have up to 3 alkyl substituents.

9. The method according to claim 3, wherein X₁ and X₂ are covalently bonded to form a polycyclic structure.

10. The method according to claim 1, additionally comprising a pharmaceutically acceptable carrier.

11. The method according to claim 1, wherein said modulator is effective at the receptor subtype A.

12. The method according to claim 1, wherein said modulator is an agonist of the receptor subtype A.

13. The method according to claim 1, wherein said administration is performed parenterally, orally, vaginally, rectally, nasally, buccally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, transdermally, intracerebroventricularly, or combinations thereof.

14. The method according to claim 1, wherein said modulator comprises a cyclopyrrolone.

15. The method according to claim 1, wherein the dose is about 0.01 to about 1000 mg.

16. The method according to claim 15, wherein the dose is about 0.1 mg to about 10 mg.

17. The method according to claim 2, wherein said modulator comprises pagoclone, suriclone, zopiclone, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, pharmaceutically acceptable salts thereof, enantiomers

thereof, or metabolites thereof.

18. The method according to claim 17, wherein the modulator comprises pagoclone.

19. The method according to claim 18, wherein the pagoclone is administered at least once daily.

20. The method according to claim 1, wherein the subject is suffering from stuttering, motor tic, clonic stuttering, dysfluency, speech blockage, dysarthria, Tourette's syndrome, or logospasm.

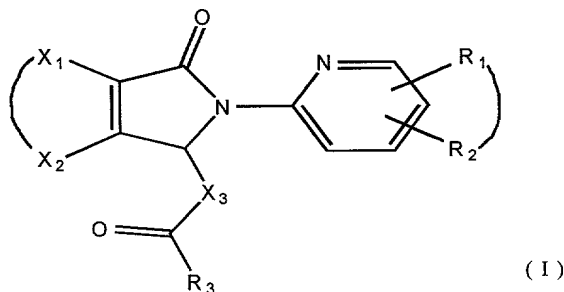
21. A method of alleviating stuttering, in a subject in need thereof, comprising:

administering a therapeutically effective dose of a gamma-amino butyric acid receptor modulator, pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof, and a second active ingredient.

22. A pharmaceutical composition for alleviating stuttering, in a subject in need thereof, comprising:

a therapeutically effective amount of a gamma-aminobutyric acid receptor modulator, its pharmaceutically acceptable salts, enantiomers, metabolites, or combinations thereof, and a second active ingredient.

23. The pharmaceutical composition according to claim 22, wherein said gamma-aminobutyric acid receptor modulator is formula I:



wherein:

(a) R_1 and R_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen; alkyl having 1 to 8 carbon atoms; alkyl having 1 to 8 carbon atoms, and having at least one of nitrogen, oxygen, sulfur, or phosphorus; aryl having 1 to 8 carbon atoms; and aryl having 1 to 8 carbon atoms and having at least one nitrogen, oxygen, sulfur, or phosphorus;

(b) R_3 is selected from the group of substituents consisting of: alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the proviso that each of the foregoing R_3 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms, aryl, alkaryl, piperazinyl, and methyl-piperazinyl;

(c) X_1 and X_2 are the same or different sterically compatible substituents which are selected from the group consisting of: hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing X_1 and X_2 substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, aminocarbonylalkyl having 2 to 4 carbon atoms; and

(d) X_3 is selected from the group consisting of: a methylene; $—C(HR_4)—$ where R_4 is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl,

alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, aryl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R₄ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; amino; —N(R₅)— where R₅ is selected from the group of substituents consisting of alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkynoxy, alkoxyalkyl, alkanoyl, alkenoyl, alkanoyloxy, alkenoyloxy, alkylsulfonyl, alkylsulfinyl, alkylthio, alkanoylamino, alkenoylamino, alkoxycarbonyl, alkenoxycarbonyl, alkoxycarbonylamino, alkoxycarbonylaminoalkyl, cycloalkyl having 3 to 6 ring members, cycloalkenyl having 4 to 6 ring members, cycloalkylalkyl having 3 to 6 ring members, cycloalkenylalkyl having 4 to 6 ring members, with the additional proviso that each of the foregoing R₅ substituents has up to 8 carbon atoms, trifluoromethyl, nitro, amino, hydroxyl, halogen, aminocarbonyl, cyano, cyanoalkyl having from 2 to 4 carbon atoms, and aminocarbonylalkyl having 2 to 4 carbon atoms; sulfur; phosphorus; and oxygen group; pharmaceutically acceptable salts thereof, enantiomers thereof, or metabolites thereof.

24. The composition according to claim 23, wherein R₁ and R₂ are covalently bonded to form a polycyclic structure.

25. The composition according to claim 23, wherein the cycloalkyl of R₃, R₄, R₅, X₁, and X₂ each have up to 3 alkyl substituents.

26. The composition according to claim 23, wherein the cycloalkenyl of R₃, R₄, R₅, X₁, and X₂ each have up to 3 alkyl substituents.

27. The composition according to claim 23, wherein the cycloalkylalkyl of R₃, R₄, R₅, X₁, and X₂ each have up to 3 alkyl substituents.

28. The composition according to claim 23, wherein the cycloalkenylalkyl of R₃, R₄, R₅, X₁, and X₂ each have up to 3 alkyl substituents.

29. The composition according to claim 23, wherein X₁ and X₂ are covalently bonded to form a polycyclic structure.

30. The pharmaceutical composition according to claim 23 wherein formula I

is a cyclopyrrolone.

31. The pharmaceutical composition according to claim 30,
wherein the cyclopyrrolone comprises pagoclone, suriclone, zopiclone, 2-(7-chloro-2-
naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-
5 naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, 2-(7-chloro-1,8-naphthyridin-
2yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone, pharmaceutically acceptable
salts thereof, enantiomers thereof, metabolites thereof, or combinations thereof.

32. The pharmaceutical composition according to claim 30,
wherein said cyclopyrrolone comprises pagoclone.

10 33. A method for alleviating stuttering, in a subject in need thereof,
comprising:

administering a dose of pagoclone in a pharmaceutically acceptable carrier, where
the pagoclone is present in an amount between about 0.1 mg and about 10 mg.

ABSTRACT

Methods of treating stuttering include treating people with gamma-aminobutyric acid (GABA) receptor modulators, including cyclopyrrolones. A second active agent may be used with GABA receptor modulators. Active enantiomers, active metabolites, and pharmaceutically acceptable salts of gamma-aminobutyric acid receptor modulators, including cyclopyrrolones, are acceptable components of the compositions. The cyclopyrrolone class of modulators includes pagoclone, suriclone, zopiclone, 2-(7-chloro-2-naphthyridin-1,8-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one, 2-(7-chloro-2-naphthyridin-1,8-yl)isoindolin-1-yl-4-acetamidobutyrate, and 2-(7-chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-5-hydroxy-2-oxohexyl)-1-isoindolinone.

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Docket No.: 112910-3300

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter claimed and for which a patent is sought on the invention entitled METHODS AND COMPOSITIONS FOR ALLEVIATING STUTTERING, the specification of which [XX] is attached hereto ☐ was filed on as Application Serial No. and was amended on (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to patentability in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

| Prior Foreign Application(s): | | | Priority Claimed | |
|-------------------------------|----------------|-----------------------------|------------------|-----------|
| <u>Number</u> | <u>Country</u> | <u>Day/Month/Year filed</u> | <u>Yes</u> | <u>No</u> |

I hereby authorize the U. S. attorneys and agents named herein to accept and follow instructions from as to any actions to be taken in the Patent and Trademark Office regarding this application without direct communication between the U. S. attorney(s) and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U. S. attorney(s) will be so notified by the undersigned.

I hereby claim the benefit under 35 USC § 119(e) of any United States provisional application(s) listed below.

| Prior Provisional Application(s): | |
|-----------------------------------|--------------------|
| <u>Application Number</u> | <u>Filing Date</u> |

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

| Prior U. S. Application(s): | | |
|-----------------------------|--------------------|---|
| <u>Serial No.</u> | <u>Filing Date</u> | <u>Status: Patented, Pending, Abandoned</u> |

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorney(s) and/or agent(s): Gilberto M. Villacorta, Reg. No. 34,038; Irah H. Donner, Reg. No. 35,120; William S. Ramsey, Reg. No. 32,715; Gianna Julian-Arnold, Reg. No. 36,358; Suresh Koshy, Reg. No. 42,761; Elizabeth Stanley, Reg. No. P44,438; and Houri Khalilian, Reg. No. 39,546 all of

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